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Cardiac Performance in Children With Homozygous Sickle Cell Disease

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Cardiac function was evaluated in 24 children from a Jamaican sickle cell cohort study. Ten patients with sickle cell disease underwent echocardiographic studies on their eighth birthday. The results were compared with 14 age- and sex-matched control children born within hours of the index patients. Left ventricular dimension index (systolic 2.89 ± 0.31 versus 2.33 ± 0.42 cm and diastolic 4.70 ± 0.35 versus 3.64 ± 0.48 cm, p = 0.001), diastolic volume (79.4 ± 17.1 versus 60.8 ± 7.8 ml, p = 0.01), left ventricular mass index (116.3 ± 3.4 versus 74.3 ± 15.2 g/m^2, p = 0.001) and cardiac index (5.51 ± 1.32 versus 3.38 ± 0.85 liters/min per m^2 p = 0.001) were significantly increased in patients with sickle cell disease compared with values in control subjects. However, there was no statistically significant difference between the two groups for ejection fraction, velocity of circumferential fiber shortening, percent fractional shortening, systolic time intervals, wall stress and ratio of wall stress-systolic volume. Although two mean ratios of wall stress-systolic volume index were lower in children with sickle cell disease as compared with control subjects (4.0 ± 0.7 versus 5.4 ± 1.7, p = 0.02 and 5.9 ± 1.2 versus 8.3 ± 2.5, p = 0.005, respectively), the range of ratios remained within normal limits (3.4 to 5.8 in children with sickle cell disease versus 2.8 to 9.5 in controls and 4.2 to 8.3 versus 3.8 to 12.5, respectively). Furthermore, only body surface area predicted group status independent of other variables (p = 0.01).

In conclusion, left ventricular contractile function remains normal in asymptomatic children with sickle cell disease in the first 8 years of life, despite an increase in end-diastolic volume.

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Adults with homozygous sickle cell disease generally manifest cardiomegaly, flow murmurs and evidence of an increased cardiac output. These changes are presumed to be part of cardiovascular adaptation to chronic anemia and there is some evidence that cardiomegaly is more marked in patients with the lowest hemoglobin levels (1). Recent prospective studies by Serjeant et al. (2) showed that hemoglobin levels of children with sickle cell disease followed up from birth decrease to levels characteristic of adults by 1 year of age. However, the age at which cardiac changes develop in sickle cell disease is unknown and the limited data available in children are inevitably derived from symptomatically biased groups of patients. This selection bias has led to conflicting results. Our study is an attempt to evaluate left ventricular function in an unbiased asymptomatic group of children with sickle cell disease.

The Jamaican sickle cell cohort study, on the basis of neonatal screening, has identified a representative sample of children with sickle cell disease who are being followed up prospectively along with age- and sex-matched control children with a normal hemoglobin genotype. Echocardiographic studies have been performed in a sample of these patients and control subjects at the age of 8 years to determine what cardiac changes are apparent by that age.

Methods

Study patients. The children were part of the Jamaican sickle cell cohort study, which includes all cases of sickle cell disease among 100,000 consecutive normal deliveries screened at the main Government Maternity Hospital (Victoria Jubilee Hospital) in Kingston, Jamaica between June 1973 and December 1981. The first 125 patients with sickle cell disease were each matched with two control groups with a normal hemoglobin genotype of the same sex who

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Table 1. Clinical and Hematologic Data

Variable	SS Disease (n = 10) (mean ± SD)	AA Controls (n = 14) (mean ± SD)	p Value
Hb (g/dl)	7.79 ± 0.64	12.0 ± 0.52	0.01
Height (cm)	122.3 ± 6.6	129.4 ± 4.2	0.01
Weight (kg)	20.8 ± 2.8	24.5 ± 1.8	0.001
BSA (m^2)	0.85 ± 0.08	0.99 ± 0.14	0.006
Systolic BP (mm Hg)	101 ± 5	97 ± 8	NS
Diastolic BP (mm Hg)	55 ± 7	60 ± 10	NS

AA = homozygous hemoglobin A; BP = blood pressure; BSA = body surface area; Hb = hemoglobin; SS = homozygous hemoglobins.

were born within hours of the index case. The diagnostic methods, methods of follow-up and techniques of hematologic procedures have been presented elsewhere (2–4). The patient's weight was measured on a lever balance with light clothing but with shoes removed, and their height was measured on a standing height stadiometer. Body surface area was estimated from nomograms derived from normal populations (Geigy statistical tables).

The study was conducted between August and October 1981, at which time the first 14 cohorts were within 2 months of their eighth birthday. Of these 14, 2 had died and 2 were living in the country remote from Kingston. Studies were performed in the remaining 10 patients. Of the 28 matched control children, 7 were unavailable (1 emigrated, 2 died, 2 were living in the country and 2 defaulted on follow-up). Appointments were given to the remaining 21, of which 14 attended.

Echocardiographic measurements. M-mode echocardiography was performed using a Smith-Kline Ekoline Ultrasonoscope 20 and a strip chart recorder. A 3.5 MHz focused (5 cm) transducer with an active crystal diameter of 1.27 cm was used. The children were examined in the supine position with the transducer along the third to fifth left sternal border. Examinations were performed by one of two cardiologists (E.C. or S.D.), neither of them aware of which children were patients and which were controls. Recordings and measurements were made according to the criteria of the American Society of Echocardiography (5). An index of agreement between measurements performed by the two cardiologists was derived from the interclass

Table 2. Measured and Derived Echocardiographic Indexes in the Two Groups

Indexes	SS Disease (mean ± SD)	AA Controls (mean ± SD)	p Value
LV end-diastolic dimension (cm)	3.99 ± 0.40	3.56 ± 0.21	0.01
LV end-systolic dimension (cm)	2.53 ± 0.28	2.31 ± 0.23	0.05
Interventricular septal thickness (cm)	0.72 ± 0.19	0.64 ± 0.10	NS
LV posterior wall (cm)	0.66 ± 0.13	0.65 ± 0.12	NS
RV anterior wall (cm)	0.27 ± 0.07	0.28 ± 0.07	NS
Aortic root (cm)	1.98 ± 0.51	1.74 ± 0.29	NS
Aortic valve opening (cm)	1.74 ± 0.25	1.54 ± 0.12	0.05
Left atrium (cm)	2.90 ± 0.33	2.46 ± 0.34	0.01
LV end-diastolic dimension index (cm/m^2)	4.70 ± 0.35	3.64 ± 0.48	0.001
LV end-systolic dimension index (cm/m^2)	2.89 ± 0.31	2.33 ± 0.42	0.001
LV systolic volume (ml)	15.3 ± 4.4	12.1 ± 4.2	NS
LVVIs (ml/m^2)	18.1 ± 4.7	12.6 ± 4.9	0.02
LV end-diastolic volume (ml)	79.4 ± 17.1	60.8 ± 7.8	0.01
LV mass (g)	99.2 ± 26.6	72.1 ± 15.4	0.01
LV mass index (g/m^2)	116.3 ± 31.4	74.3 ± 15.2	0.001
Cardiac index ($liters/m^2$)	5.51 ± 1.32	3.38 ± 0.85	0.001

LV = left ventricular; LVVIs = left ventricular systolic volume index; RV = right ventricular; other abbreviations as in Table 1.

correlation coefficient utilizing Fisher's analysis of variance. There was a good agreement between interobserver measurements for left ventricular diastolic dimension (correlation coefficient r = 0.99, p = 0.001 and a mean absolute difference between determinations of 1%), systolic dimension (r = 0.98, p = 0.001 and a mean absolute difference of 1%), posterior wall and septum (r = 0.86, p = 0.001 and a mean absolute difference of 0.6%), left atrial size (r = 0.999, p = 0.001, a mean absolute difference of 0.2%), aortic root (r = 0.98, p = 0.001, a mean absolute difference 1.4%) and right ventricular diastolic dimension (r = 0.81, p = 0.001, a mean absolute difference of 3.2%).

The left ventricular dimensions were measured from a point just below the mitral leaflets at the level of the chordae tendineae. The left ventricular end-diastolic dimension (Dd) was measured at the onset of the QRS complex of the electrocardiogram, and the systolic dimension at the point of maximal posterior movement of the ventricular septum.

Left ventricular end-diastolic volume and ejection fraction were estimated by the methods of Meyer et al. (6). Left ventricular end-diastolic volume (LVEDV) was estimated from the regression equation

$$\text{LVEDV} = -19.1 + 14.6\ \text{Dd} + 0.62\ \text{Dd}^3,$$

where Dd represents left ventricular end-diastolic dimension (6).

Left ventricular ejection fraction (LVEF) was estimated from the formula

$$\text{LVEF} = 1-(\text{As/Ad}) \times (\text{Ds/Dd}^2),$$

where As/Ad is the ratio of end-systolic and end-diastolic left ventricular major axis dimensions and is assumed to be 0.9, corresponding to a 10% shortening of this axis and Ds represents the left ventricular end-systolic dimension (6).

Left ventricular mass (LV mass) was calculated from the cube method as follows (7):

$$\text{LV mass} = (1.05)\ [(\text{LVDd} + \text{IVS} + \text{LVPW})^3 - (\text{LVDd})^3],$$

where IVS is the wall thickness of the interventricular septum, LVPW is thickness of left ventricular posterior wall and LVDd is the minor axis left ventricular diameter, all taken at end-diastole (5).

Cardiac output was calculated from the stroke volume and heart rate (the stroke volume was derived from the product of left ventricular end-diastolic volume and ejection fraction).

Systolic time intervals were calculated from the echocardiographic recordings, with the left ventricular ejection time being defined as the interval between opening and closing of the aortic valve, and the left ventricular pre-ejection period as the time from the Q wave of the electrocardiogram to the start of the opening of the aortic valve (8). Right ventricular ejection time and pre-ejection period were similarly calculated from the pulmonary valve echogram and the electrocardiogram.

Left ventricular end-systolic wall stress was calculated by the method of Reicheck et al. (9). End-systolic stress index was calculated by the method of Quinones et al. (10). Stress to volume and stress-volume index ratios were then determined.

Statistics. Statistical analysis for comparison between patients and control subjects was performed using Student's

Table 3. Left Ventricular Function Indexes in the Two Groups

Indexes	SS Disease (mean ± SD)	AA Controls (mean ± SD)	p Value
Heart rate	95 ± 9	87 ± 14	NS
Fractional shortening (%)	37 ± 6	35 ± 4	NS
Circumferential fiber shortening (circ/s)	1.29 ± 0.23	1.25 ± 0.19	NS
LV ejection fraction (%)	63 ± 6	62 ± 5	NS
End-systolic stress ($\times 10^3$ dynes/cm^2)	70 ± 17	65 ± 23	NS
End-systolic stress index (mm Hg)	103 ± 15	95 ± 21	NS
ESS/LVV	4.8 ± 1.1	5.4 ± 1.1	NS
ESS/LVVI	4.0 ± 0.7	5.4 ± 1.7	0.02
ESI/LVV	7.1 ± 1.8	8.4 ± 2.0	NS
ESI/LVVI	5.9 ± 1.2	8.3 ± 2.5	0.005
RVPEP/RVET	0.23 ± 0.05	0.22 ± 0.04	NS
LVPEP/LVET	0.29 ± 0.02	0.29 ± 0.03	NS

circ = circumference; ESI/LVV = end-systolic stress index and left ventricular systolic volume ratio; ESI/LVVI = end-systolic stress index and left ventricular systolic volume index ratio; ESS/LVV = end-systolic stress and left ventricular systolic volume ratio; ESS/LVVI = end-systolic stress and left ventricular systolic volume index; LV = left ventricular; LVPEP/LVET = left ventricular pre-ejection period and ejection time ratio; RVPEP/RVET = right ventricular pre-ejection period and ejection time ratio; other abbreviations as in Table 1.

t test and analysis of variance. Significant difference was defined as a probability (p) value ≤ 0.05.

Results

Clinical data. There were 10 children with sickle cell disease (6 male, 4 female) and 14 control children (8 male, 6 female) all of whom were within 2 months of their eighth birthday at the time of study. Hematologic and anthropometric data (Table 1) indicate significantly lower hemoglobin levels, height, weight and body surface area in the children with sickle cell disease.

Echocardiographic data. Cardiac measurements and derived indexes are shown in Table 2 and details of left ventricular function and systolic time intervals in Table 3. Left ventricular systolic and diastolic dimensions, aortic valve opening and left atrial size were significantly increased in children with sickle cell disease. The derived indexes of left ventricular end-diastolic volume, left ventricular end-diastolic minor axis dimension index, left ventricular mass and cardiac index were all significantly greater in the children with sickle cell disease.

Ventricular function. There were weak but significant negative correlations between hemoglobin level and cardiac index in both patients and controls ($p = 0.05$), but no significant correlations between hemoglobin and end-diastolic volume, ejection fraction or pulse rate. Furthermore, there was no statistical significance in indexes of cardiac function between the two groups (Table 3), except for the ratio between end-systolic wall stress and left ventricular systolic volume index ($p = 0.02$) and the ratio between end-systolic stress index and left ventricular systolic volume index ($p = 0.005$). Of all the variables indicated, only body surface area significantly predicted group status independent of other variables ($p = 0.01$).

Discussion

Echocardiography is a simple noninvasive tool for assessing cardiac dimensions and function. Its indirect nature implies that approximations are necessary in some measurements and that indexes must be derived from complex formulas rather than direct measurements. These formulas have generally been well substantiated from autopsy, angiographic and hemodynamic data. Within these limitations, echocardiography gives very useful information that would not otherwise be available.

Previous studies. Cardiac size and function in sickle cell disease have been previously studied (11–15) by echocardiography and by radionuclide ventriculography (16,17). Most of these studies were performed on adults and only one (12) was confined to children. From these studies, there is general agreement that cardiac dimensions, left ventricular volume and mass and cardiac output are increased in subjects with sickle cell anemia. These observations are consistent, regardless of age. However, the age at which cardiac enlargement develops is unknown, although it may well be in the first few years of life. Our study has shown that in patients with sickle cell anemia, left ventricular diastolic and systolic dimensions and dimension index, diastolic volume, left ventricular mass and cardiac index are significantly increased by the age of 8 years compared with values in control subjects (Table 2).

Ventricular function variables. Data on indexes of left ventricular function, however, are conflicting. Ejection fraction in most adult studies has been normal (11,14–17), although Val-Mejias et al. (13) noted ejection fraction to be normal in patients under 23 years of age but to decrease after this age. Velocity of circumferential fiber shortening, percent shortening and systolic time indexes in these adult studies have also been predominantly normal. In our study, ejection fraction, velocity of circumferential fiber shortening, percent fractional shortening, systolic time indexes, wall stress and wall stress-systolic volume ratios were found to be similar to those of age-matched control children with normal hemoglobin.

The study by Rees et al. (12) stands in sharp contrast to this general experience. In a group of 44 children with sickle cell disease aged 2 to 14 years, compared with 28 randomly selected normal black children of comparable age, ejection fraction, circumferential fiber shortening and percent fractional shortening were significantly reduced in the sickle cell group. Further analysis indicated that this difference was entirely due to a symptomatic subgroup of 35 children who reported dyspnea or fatigue, or both, at rest or during mild activity. On the other hand, indexes of nine asymptomatic children with sickle cell disease did not differ from those in the control group. The conflict between apparently normal studies of cardiac function in adults and the high prevalence of abnormal function noted by Rees et al. (12) in children could only be reconciled by improving cardiac function with age, death of the severely affected children so that only those with normal function survive or selection biases resulting in unusually severely affected children or unusually mildly affected adults. The first explanation is pathologically unlikely and the second would require a high mortality rate from cardiac causes among children, a trend that has not been observed (1,2,18,19). The apparently normal cardiac function in a representative sample of 10 subjects with sickle cell disease in our study raises the question of a symptomatic bias in the patients studied by Rees et al. (12). Is it possible that a substantial proportion of children were referred for the investigation of cardiac symptoms? Although our present study is small, the method of ascertainment yields information that is not subject to such biases.

Implications. Our study, along with others performed in adult groups, suggests that despite increased cardiac dimensions and cardiac output in sickle cell disease, left ven-

tricular function is generally normal. This conclusion is based on ejection fraction, velocity of circumferential fiber shortening, percent fractional shortening and systolic time indexes that do not differ significantly from those in control groups. Use of systolic time indexes as an indicator of left ventricular function was questioned by Denenberg et al. (15), who suggested that under the altered loading conditions of chronic anemia, a normal ejection fraction may be maintained even in the presence of compromised left ventricular function. These authors argued that cardiac dilation increased preload and that decreased peripheral resistance reduced the afterload, both factors tending to increase ejection fraction. They recommended that more appropriate indicators of left ventricular function independent of time intervals should be utilized instead. Using rest end-systolic stress-systolic volume index and the slope of end-systolic stress versus end-systolic volume index relation as indicators of left ventricular performance, Sagawa et al. (20) found both to be significantly decreased in patients with sickle cell disease compared with controls.

Our data on mean end-systolic wall stress-systolic volume index and end-systolic stress index-systolic volume index ratios confirm these findings. However, only body surface area significantly predicted group status independent of other variables ($p = 0.01$). All the ratios from children with sickle cell disease were within a normal range (3.4 to 5.8 for patients versus 2.8 to 9.2 for control subjects for end-systolic stress/left ventricular volume index and 4.2 to 8.3 for patients versus 3.8 to 12.5 for control subjects for end-systolic stress index/left ventricular volume index). Although the respective mean ratios were statistically lower in children with sickle cell disease compared with control subjects (Table 3), it appears that in this group of patients, left ventricular performance remains within a normal range up to 8 years of age.

Future directions. Although the numbers are small, our study has made an attempt to exclude a symptomatic bias. More large scale studies on cardiac function in both children and adults with sickle cell disease are needed, however, and these should use alternatives to the systolic time indexes, which may be unreliable in the presence of chronic anemia. End-systolic wall stress and end-systolic stress index normalized to left ventricular systolic volume index are promising markers of ventricular function. Longitudinal studies of these indexes may clarify the natural history of left ventricular performance in children and adults with sickle cell anemia.

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